

Pattern of cognitive deficits in severe COVID-19

The severe form of COVID-19 tends to be associated with neurological deficits.^{1,2} Among patients with acute respiratory distress syndrome (ARDS), who benefited from mechanical ventilation and were examined after discontinuation of sedation and neuromuscular blockade, 69% presented agitation, 65% confusion, 67% corticospinal tract signs and 33% dysexecutive syndrome.²

We describe here the pattern of cognitive deficits in a series of 13 consecutive inpatients hospitalised in the Lausanne University Hospital, whom we examined during the post-critical acute stage of severe COVID-19 (table 1). Inclusion criteria were COVID-19 diagnosed by PCR and ARDS that required intubation and mechanical ventilation in intensive care unit (ICU). Exclusion criteria were prior psychiatric or neurological diseases, including neurocognitive impairment or dementia. At the time of testing, patients were no longer sedated and ICU delirium symptoms, which were present in seven patients, resolved in six of them (P5–P7, P10, P11, P13) or subsided to a great extent (P12).

The neuropsychological evaluation comprised two standardised test batteries. The Montreal Cognitive Assessment (MoCA; <https://www.mocatest.org>),

which covers main cognitive functions, revealed normal cognitive performances in four patients (table 1; P1–P4), mild deficits in four (P5–P8) and moderate to severe deficits in five (P9–P13). MoCA subtests revealed selective cognitive pattern with lower performances in executive functions for patients with normal MoCA scores and more extensive cognitive impairment in executive, memory, attentional and visuospatial functions, with relatively preserved orientation and language, for patients with mild to severe MoCA deficits.

The Frontal Assessment Battery (FAB; www.psychdb.com/cognitive-testing/fab) revealed executive dysfunction in eight patients (table 1; P6–P13). Among the FAB subtests, the most affected was lexical fluency, impaired in all patients except in one (with normal MoCA: P3).

Pearson (r) and Spearman (rho) correlation analyses were conducted. MoCA and FAB scores were correlated ($r=0.88$; $p<0.001$). Mental fatigue and cognitive slowness, assessed with observational scales, correlated with MoCA (respectively: $\rho=-0.67$; $p=0.012$; $\rho=-0.74$; $p=0.004$) and FAB scores (respectively: $\rho=-0.85$; $p<0.001$; $\rho=-0.72$; $p=0.006$). Age correlated with FAB ($r=-0.591$; $p=0.033$) but not with MoCA scores. There was no significant correlation between MoCA or FAB scores and the following measures:

gender, length of ICU stay, duration of mechanical ventilation, delay between ICU discharge and cognitive assessment, mood and anxiety disturbances. Mood disturbance, assessed in self-report, was considerable (table 1; $\geq 5/10$) in 38% of patients and 23% reported anxiety about breathing difficulties, fear of dying or reminiscences of intensive care. Seven patients presented ICU delirium (table 1); its occurrence was correlated with MoCA score ($\rho=-0.619$; $p=0.024$) and cognitive slowness ($\rho=0.585$; $p=0.036$), but not with FAB, length of ICU stay, duration of mechanical ventilation, delay between ICU discharge and cognitive assessment, age, gender, mental fatigue, mood and anxiety disturbances.

Eleven patients had brain imaging. None of them sustained acute stroke or ischaemic damage; among the eight patients who had MRI-based morphometry, focal brain atrophy was, however, present in patients with normal (table 1; P1) or deficient performance at MoCA (P10–P13) as it was absent in patients with normal (P3, P4) or deficient performance at MoCA (P7). Four patients had lumbar puncture, revealing enhanced proteinorachia (P3, P11, P13) and barrier index (P11, P13) or normal values (P12).

Two cognitive profiles characterise the post-critical acute phase of severe COVID-19: (1) normal score at MoCA, but tendency for lower performances in

Table 1 Patient (P1–P13) characteristics and performance in cognitive tests

| Patients | Age (years) | Sex | ICU stay (days) | Mechanical ventilation (days) | ICU discharge to cognitive assessment (days) | Brain atrophy | ICU delirium | MoCA scores (0–30) | FAB scores (0–18) | MoCA mean subtest scores (0–6) | FAB mean subtest scores (0–3) | Cognitive slowness (0–3) | Mental fatigue (0–3) | Mood (0–10) and anxiety* disturbances |
|----------|-------------|-----|-----------------|-------------------------------|--|----------------------------------|--------------|--------------------|-------------------|----------------------------------|-----------------------------------|--------------------------|----------------------|---------------------------------------|
| P1 | 60s | m | 46 | 38 | 4 | rFgm; fv | N | 29 | 16.8 | Ex: 3.63 Me: 5.10 VS: 5.63 | Fl: 1.75 Co: 2.50 Pr: 2.75 | 1 | 2 | 8* |
| P2 | 60s | f | 12 | 11 | 6 | – | N | 28 | 15.6 | La: 5.70 At: 5.75 Or: 6.00 | Int: 3.00 | 2 | 2 | 2 |
| P3 | 70s | m | 31 | 21 | 6 | None | N | 26.9 | 15.6 | Ex: 5.75 Me: 5.00 VS: 5.40 | Fl: 1.25 Co: 2.00 Pr: 2.50 | 0 | 2 | 3 |
| P4 | 60s | m | 67 | 50 | 10 | None | N | 26 | 14.4 | La: 5.70 At: 5.75 Or: 6.00 | Int: 3.00 | 1 | 2 | 1 |
| P5 | 60s | m | 16 | 10 | 9 | None | Y | 23 | 16.8 | Ex: 2.25 Me: 3.00 At: 3.75 | Fl: 1.25 Co: 2.00 Pr: 2.50 | 2 | 1 | 5 |
| P6 | 50s | m | 21 | 16 | 7 | – | Y | 22 | 13.2 | VS: 4.13 Or: 5.25 La: 5.40 | Int: 2.75 | 2 | 2 | 0 |
| P7 | 50s | m | 21 | 17 | 5 | None | Y | 21 | 14.4 | Ex: 2.25 Me: 3.00 At: 3.75 | Fl: 1.25 Co: 2.00 Pr: 2.50 | 2 | 2 | 3 |
| P8 | 70s | f | 14 | 13 | 4 | None | N | 19 | 9.6 | La: 5.40 | Int: 2.75 | 1 | 2 | 2* |
| P9 | 60s | m | 21 | 17 | 4 | None | N | 17 | 7.2 | Me: 0.48 VS: 1.13 Ex: 1.30 | Fl: 0.00 Inh: 0.80 Pr: 0.80 | 3 | 3 | 8* |
| P10 | 60s | m | 27 | 19 | 2 | rIFgm; rIFgm; rIFwm; rlv; tv; fv | Y | 16.8 | 2.4 | At: 2.00 Or: 3.40 La: 4.08 | Int: 1.00 Co: 1.60 | 3 | 3 | 3 |
| P11 | 50s | m | 40 | 23 | 2 | rIFgm; rICgm | Y | 13 | 9.6 | | | 2 | 2 | 2 |
| P12 | 70s | m | 25 | 25 | 7 | rFgm; rIFwm; lPwm; rIOWm | Y | 10 | 4.8 | | | 3 | 3 | 8 |
| P13 | 70s | f | 24 | 19 | 6 | rIFgm; rFgm; rITgm; rlv; tv | Y | 4 | 1.2 | | | 3 | 3 | 6 |
| MEAN: | 64.8 | | 28.1 | 21.5 | 5.5 | | | 19.7 | 10.9 | | | 1.9 | 2.2 | 3.9 |
| SD: | 7.6 | | 15.2 | 11.2 | 2.4 | | | 7.5 | 5.5 | | | 1.0 | 0.6 | 2.8 |

Patients were ranked from highest to lowest performing at MoCA test. Three patients had a CT scan, which was within normal range (P5, P8, P9); eight patients had an MRI-based morphometry, which was within normal range in three patients (P3, P4, P7) and showed signs of atrophy, in bold, in five other patients (P1, P10–P13). ICU delirium was rated N (no delirium) or Y (with delirium). Scores at MoCA and FAB: performance within normal limits is in italics, deficient in bold. For the MoCA, the maximum score is 30 and deficient score below 26 (see <https://www.mocatest.org> for details); four patients (P1–P4) had normal performances (score ≥ 26), four patients (P5–P8) had mild deficits (score between 25 and 18) and five patients (P9–P13) had moderate to severe deficits (score below 18). For the FAB, the maximum score is 18. The cut-off score of normal performance is determined by age and educational level (see www.psychdb.com/cognitive-testing/fab for details). The subtest environmental autonomy not having been evaluated because of sanitary requirements, we have extrapolated for the missing subtest by multiplying the FAB score by 1.2. For each MoCA subtest (At: attention, Ex: executive functions, La: language, Me: memory, Or: orientation, VS: visuospatial abilities) and FAB subtest (Co: conceptualisation, Fl: mental flexibility, Inh: inhibitory control, Int: sensitivity to interference, Pr: programming) means were calculated within three groups of patients: normal performance at MoCA score (mean P1–P4), mild deficits at MoCA score (mean P5–P8), moderate to severe deficits at MoCA score (mean P9–P13). Cognitive slowness and mental fatigue were rated on an observational scale of 3 (3 corresponding to a severe manifestation). Mood disturbance was rated on a self-assessment scale of 10 (10 corresponding to most affected) and anxiety with a yes/no question (yes=present*). Last two rows: mean and SD. C, cingulate gyrus; f, female; F, frontal gyrus; FAB, Frontal Assessment Battery; fv, fourth ventricle; gm, grey matter; ICU, intensive care unit; l, left; lv, left ventricle; m, male; MoCA, Montreal Cognitive Assessment; O, occipital gyrus; P, parietal gyrus; r, right; rv, right ventricle; T, temporal gyrus; tv, third ventricle; wm, white matter.

executive than in other cognitive functions; (2) mild to severe deficits at MoCA with extensive cognitive impairment in executive, memory, attentional and visuospatial functions, but relatively preserved orientation and language, executive dysfunction being confirmed by the FAB score. These cognitive profiles together with mood and anxiety disturbances, which we observed in the acute stage, in the absence of stroke, are reminiscent of those reported in the aftermath of ARDS of other aetiologies, where up to 70% of ARDS survivors had presented at hospital discharge cognitive deficits, affecting predominantly attention, mental processing speed, memory and executive functions,^{3–5} with a high prevalence of depression and anxiety.⁵

Furthermore, cognitive impairment in severe COVID-19, as in ARDS of other aetiologies,⁵ does not correlate with length of mechanical ventilation or length of ICU stay and thus severity of the acute illness. However, the occurrence of ICU delirium tends to be associated with poorer cognitive performance.¹

Structural damage, such as ischaemic or hypoxic lesions of the hippocampus, basal ganglia or cerebellum lesions as well as brain atrophy (in particular hippocampal) or disruption of functional connectivity, which occur frequently in ARDS survivors,^{3,4} may contribute to cognitive dysfunction. In the context of COVID-19, stroke and perfusion abnormalities have been reported,^{1,2} but were excluded here in all 11 patients, who had brain imaging during the acute stage.

Prior brain atrophy may confer worse outcome as shown for the risk to develop delirium and cognitive disorders in ARDS of other aetiologies.^{3,4} Patchy grey and/or white matter atrophy was present in five patients (of the eight who had MRI), most likely reflecting a prior condition; it was associated with cognitive impairment in four patients. However, brain atrophy did not always induce cognitive impairment and conversely, cognitive impairment was also present without imaging abnormalities, as in previous non-COVID-19 studies.⁴

Our sparse data on cerebrospinal fluid suggest that increased blood–brain barrier

permeability may contribute to neurological symptoms, as previously described for mild central nervous system inflammation in ICU patients.¹

In conclusion, pattern of cognitive deficits, present during the acute stage in our 13 patients without history of cognitive, psychiatric or neurological disorders, is probably linked to critical illness as part of ARDS due to COVID-19, since it is very similar to those reported in ARDS of other aetiologies. Further investigations are needed to determine predictive factors and underlying neural mechanisms, and clarify with a long-term follow-up whether patients will completely recover.

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